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Trends over time in congenital malformations in live-born children conceived after assisted reproductive technology

ANNA-KARINA A. HENNINGSEN[1], CHRISTINA BERGH[2], ROLV SKJAERVEN[3,4], AILA TIITINEN[5], ULLA-BRITT WENNERHOLM[6], LIV B. ROMUNDSTAD[7,8,9], MIKA GISSLER[10,11], SIGNE OPDAHL[8,9], ANDERS NYBOE ANDERSEN[1], ØJVIND LIDEGAARD[12], JULIE L. FORMAN[13] & ANJA PINBORG[14]

[1]Fertility Clinic, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark, [2]Department of Obstetrics and Gynecology, Institute of Clinical Sciences, Sahlgrenska Academy, University of Gothenburg, Reproductive Medicine, Sahlgrenska University Hospital, Gothenburg, Sweden, [3]Department of Global Public Health and Primary Health Care, University of Bergen, Bergen, [4]Medical Birth Registry of Norway, Norwegian Institute of Public Health, Bergen, Norway, [5]Department of Obstetrics and Gynecology, University of Helsinki, Helsinki University Hospital, Helsinki, Finland, [6]Perinatal Center, Department of Obstetrics and Gynecology, Institute of Clinical Sciences, Sahlgrenska Academy, Gothenburg University, Sahlgrenska University Hospital/East, Gothenburg, Sweden, [7]Spiren Fertility Clinic, Trondheim, [8]Central Norway Regional Health Authority, Stjørdal, [9]Department of Public Health and General Practice, Norwegian University of Science and Technology, Trondheim, Norway, [10]National Institute for Health and Welfare (THL), Helsinki, Finland, [11]Department of Neurobiology, Care Sciences and Society, Division of Family Medicine, Karolinska Institute, Stockholm, Sweden, [12]Gynecological Clinic, Rigshospitalet, University of Copenhagen, Copenhagen, [13]Section of Biostatistics, Department of Public Health, University of Copenhagen, Copenhagen, and [14]Department of Obstetrics and Gynecology, Hvidovre Hospital, University of Copenhagen, Copenhagen, Denmark

Key words
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Correspondence
Anna-Karina A. Henningsen, Fertility Clinic, Rigshospitalet, Copenhagen University Hospital, Blegdamsvej 9, 2100 Copenhagen, Denmark.
E-mail: ahen0024@regionh.dk

Conflict of interest
The authors have stated explicitly that there are no conflicts of interest in connection with this article.

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Abstract

Introduction. Children born after assisted reproductive technology, particularly singletons, have been shown to have an increased risk of congenital malformations compared with children born after spontaneous conception. We wished to study whether there has been a change in the past 20 years in the risk of major congenital malformations in children conceived after assisted reproductive technology compared with children spontaneously conceived. *Material and methods.* Population-based cohort study including 90 201 assisted reproductive technology children and 482 552 children spontaneously conceived, born in Denmark, Finland, Norway and Sweden. Both singletons and twins born after in vitro fertilization, intracytoplasmatic sperm injection and frozen embryo transfer were included. Data on children were taken from when the national Nordic assisted reproductive technology registries were established until 2007. Multiple logistic regression analyses were used to estimate the risks and adjusted odds ratios for congenital malformations in four time periods: 1988–1992, 1993–1997, 1998–2002 and 2003–2007. Only major malformations were included. *Results.* The absolute risk for singletons of being born with a major malformation was 3.4% among assisted reproductive technology children vs. 2.9% among children spontaneously conceived during the study period. The relative risk of being born with a major congenital malformation between all assisted reproductive technology children and children spontaneously conceived remained similar through all four time periods ($p = 0.39$). However, we found that over time the number of children diagnosed with a major malformation increased in both groups across all four time periods. *Conclusion.* When comparing children conceived after assisted reproductive technology and spontaneously conceived, the relative risk of being born with a major congenital malformation did not change during the study period.

Abbreviations: aOR, adjusted odds ratio; ART, assisted reproductive technology; CI, confidence interval; EUROCAT, European Concerted Action on Congenital Anomalies and Twins; ICD, International Classification of Diseases; ICSI, intracytoplasmatic sperm injection; IVF, in vitro fertilization; SC, spontaneous conception.

Introduction

Children born after assisted reproductive technology (ART), particularly singletons, have an increased risk of malformations when compared with spontaneously conceived (SC) children (1–6). This is clinically important, but whether it is a consequence of the parental characteristics related to subfertility or the ART methods themselves remains unresolved. To improve our understanding of the mechanisms behind malformations, it has recently been argued that a classification of malformations based on pathology and etiology rather than according to organ system would be more correct (7,8). However such a classification of malformations is currently only feasible in a few countries. Recently, the risk of several adverse perinatal outcomes has been found to decrease over time for both singletons and twins conceived after ART in the Nordic countries (9). This can to some extent be explained by a change in the population of couples undergoing ART, together with many clinical and laboratory improvements over the years. Therefore we wished to investigate whether this trend could also be seen for congenital malformations.

In the present study, we aimed to assess the risk of major malformations in children conceived after ART compared with SC children. Furthermore, we wished to investigate whether there had been a change in the risk of major congenital malformations in ART children during a 20-year period. Malformations were grouped according to organ system. Furthermore, we addressed the risk of malformations over time with trend analyses during the following time periods: 1988–1992, 1993–1997, 1998–2002 and 2003–2007.

Material and methods

Data sources

We used a Nordic population-based cohort of all ART singletons (n = 61 281) and twins (n = 28 920) from Denmark, Finland, Norway and Sweden. Data were included from the year each national ART register was established until December 2007 (Table S1) (10). Only children with a gestational age of 22^{+0} weeks or more were included. ART children included singletons and twins born after in vitro fertilization (IVF), intracytoplasmic sperm injection (ICSI) and frozen embryo transfer. The ART singletons were matched 1:4 with a comparison group of SC children from their own country. The matching criteria were parity (0 vs. ≥1) and year of birth. To ensure a sufficiently large number of SC twins, all SC twins born during the study period were included. Ovulation induction and intrauterine insemination have only recently been registered in the Nordic ART registers. Accordingly, children conceived after these techniques began to be used, may appear among the controls. Some of our data have previously been published as part of national cohorts (2,11–22).

Registration and classification of malformations

In Denmark, data on malformations were retrieved from the National Patient Registry. In Finland, data on malformations originate from the Registry of Congenital Malformations. In Norway data on malformations were retrieved from the Medical Birth Registry and, since 1998, also from the children's clinics. In Sweden, the malformation diagnoses were retrieved both from the Medical Birth Registry and the National Patient Registry. This means that except for Norway in the early study period, malformation diagnoses were not just retrieved at birth. Since only major malformations were included, it seems most likely that the malformations would be detected regardless of conception method. Only live-born children were included. Stillborn children were excluded due to questionable quality and consistency in the registration of malformations in stillborn children in countries not having a specific malformation registry.

Key Message

Although children conceived after assisted reproductive technology have an increased risk of being born with a congenital malformation, their relative risk of major congenital malformations did not increase over time in comparison with children born after spontaneous conception.

Information on terminations of pregnancy due to a malformation was not available. In each country, malformations were coded using the International Classification of Diseases (ICD). Sweden used ICD-8 from 1982 to 1986, ICD-9 from 1987 to 1996 and ICD-10 from 1997 and onwards. Norway used ICD-8 until 1998 and ICD-10 from 1999. Finland used the extended ICD-9 classification for malformations. Denmark used the ICD-10 during the entire study period. The European Surveillance of Congenital Anomalies (European Concerted Action on Congenital Anomalies and Twins, EUROCAT) classification system was used to differentiate between major and minor malformations. All minor malformations were excluded (23).

Statistical analyses

Multiple logistic regression analyses were used to estimate the odds ratios (OR) for malformations. Crude singleton analyses were adjusted for the matching criteria: parity (0 vs. ≥1) and year of birth, and further adjustment was made for maternal age (<30, 30–34, 35–39, ≥40 years), child sex, and country. To be able to compare results between singletons and twins, we decided to perform identical analyses for singletons and twins. All regression analyses of twin data were further adjusted for correlation within twin pairs, for example, by using generalized estimating equations to fit the logistic regression models. To compare only dizygotic twins, we performed opposite-sex twin analyses. To investigate the trends over time, data were stratified into four periods: 1988–1992, 1993–1997, 1998–2002 and 2003–2007. To assess whether the risk patterns between the conception groups changed over time, we tested group–time interaction terms. All results presented are based on Nordic data. Statistical tests were declared significant for a two-sided *p*-value not exceeding 0.05. All analyses were performed using SAS statistical software, version 9.4 (SAS Institute).

Ethical approval

The study was approved by the Data Protection Agencies and the authorities keeping the registry in each participating country. Permission from the ethical committees was given in Sweden (Dnr 023-09, T431-09) and in Norway (REK 2010/1909-11). Denmark and Finland require no such permission for registry research.

Results

Maternal and birth characteristics

For both singletons and twins, mothers of ART children were considerably older than women who conceived spontaneously. The singleton mothers were matched on parity but among twins, 69.5% of the ART mothers were nulliparous compared with only 39.0% of the control mothers (Table 1). When testing the impact of our confounders, we found that children born to primiparous women had an increased risk of being born with a major malformation compared with children of multiparous women (OR 1.23, 95% CI 1.12–1.28). Boys also had a higher risk of malformation compared with girls (OR 1.10, 95% CI 1.08–1.13).

Table 1. Characteristics of mothers and their children according to mode of conception and multiplicity.

	Singletons		Twins	
	ART (*n* = 61 281)	SC (*n* = 350 811)	ART (*n* = 28 920)	SC (*n* = 131 741)
Maternal age (mean ± SD)	33.4 ± 4.1	28.5 ± 5.1	32.8 ± 3.9	30.1 ± 4.9
<30, *n* (%)	11 133 (18.7)	207 855 (60.0)	6278 (22.3)	61 255 (47.1)
30–34, *n* (%)	24 650 (41.4)	96 728 (27.9)	12 595 (44.9)	44 862 (34.5)
35–39, *n* (%)	19 800 (33.3)	35 627 (10.3)	8189 (29.2)	20 724 (15.9)
≥40, *n* (%)	3913 (6.6)	6521 (1.9)	1010 (3.6)	3222 (2.5)
Nulliparous, %	70.1	69.5	69.5	39.0
Cesarean section, %	23.1	14.2	49.1	39.7
Boys, %	51.5	51.2	51.3	49.4
Birthweight (mean ± SD)	3440 ± 627	3507 ± 562	2524 ± 614	2567 ± 612
Gestational age (mean ± SD)	276 ± 16	279 ± 13	254 ± 21	256 ± 20
Birthweight <2500 g, *n* (%)	3647 (6.0)	12 821 (3.7)	12 340 (43.1)	51 889 (39.8)
Birthweight <1500 g, *n* (%)	815 (1.3)	2096 (0.6)	1865 (6.5)	7946 (6.1)
Preterm birth <37 weeks, *n* (%)	5157 (8.4)	19 583 (5.6)	13 513 (46.7)	56 247 (42.7)
Preterm birth <32 weeks, *n* (%)	1002 (1.6)	3379 (1.0)	2437 (8.4)	9858 (7.5)
Small for gestational age, *n* (%)	2265 (3.7)	10 482 (3.0)	4377 (15.3)	20 694 (15.9)

ART, assisted reproductive technology; SC, spontaneous conception.

Assisted reproductive technology singletons had a lower mean birthweight than SC singletons (3440 g vs. 3507 g, respectively) and a three-day shorter gestational age (276 days vs. 279 days). Overall, the risk of adverse perinatal outcomes was higher in ART singletons than in their controls. For twins, a similar pattern was found, although the differences between ART and controls were much smaller (Table 1).

Risk of malformations

Among singletons a major malformation was observed in 2100 (3.4%) ART children vs. 10 223 (2.9%) SC children [adjusted odds ratio (aOR) 1.14, 95% CI 1.08–1.20]. The relative risk of being born with a major malformation was 1.18 for ART singletons. They had an increased risk of malformations in the following organ systems: nervous system (aOR 1.39, 95% CI 1.04–1.85); eye (aOR 1.54, 95% CI 1.12–2.10); ear, face and neck (aOR 1.22, 95% CI 1.02–1.47); heart (aOR 1.18, 95% CI 1.05–1.33), gastrointestinal system (aOR 1.29, 95% CI 1.07–1.54); urinary system (aOR 1.35, 95% CI 1.11–1.64); musculo-skeletal system (aOR 1.11, 95% CI 1.03–1.20) (Table 2).

Among twins, 1528 (5.3%) ART and 5822 (4.4%) SC children had a major malformation. The relative risk of being born with a major malformation was 1.24 for ART twins. When adjusting for known confounders, parity and maternal age were of particular importance for the risk of major malformations. After adjustments, ART twins had the same risk of being born with a major malformation as SC twins (aOR 0.95, 95% CI 0.88–1.01) (Table 2). Similarly, in the analyses restricted to opposite-sex twins, where only dizygotic twins from both conception groups were considered, there was no difference in risk of major malformations between ART and SC twins (aOR 1.00, 95% CI 0.90–1.11).

Trends over time

The relative risk of being born with a major congenital malformation between ART children and SC children remained similar in all four time periods ($p = 0.39$). This was also the case when analyzing the trends over time for singletons ($p = 0.43$) and twins ($p = 0.18$) separately. However, we found that over time the number of children diagnosed with a major malformation increased in both groups (Table 3). After adjustment for maternal age, parity, year of birth, child's sex, and country, the increase in risk from the first to the last period had an aOR of 1.54 (95% CI 1.22–1.94) among ART children and aOR of 1.60 (95% CI 1.47–1.74) among SC children.

Country-specific analyses

When performing separate analyses on national data, there were overall no differences between the four Nordic countries, but ART singletons consistently had a higher risk of being born with a major malformation compared with SC singletons (data not shown).

Discussion

The main finding in this large matched cohort study, based on data on children born after ART in four Nordic countries during a 20-year period, was that the relative risk of being born with a major malformation remained unchanged for ART children compared with SC children. We also confirmed that ART singletons had a slightly increased risk of being born with a major congenital malformation (3,5,6).

However, the absolute risk of being born with a major congenital malformation increased over time for both singletons and twins, regardless of mode of conception. This is despite a longer follow-up time for the children born in the early years. We believe that this finding is most likely due to national improvements in data quality, based on the increased registration and ascertainment of malformations during the study period. Country-specific analyses have shown that a consequence of the improvements in the national registration system for malformations is a significant increase in the annual number of malformations registered for both children born after ART as well as SC.

We found that ART twins had a similar risk of being born with a major congenital malformation compared with SC twins. When using Weinberg's differential rule, it was estimated that only 3.5% of the ART twins were monozygotic vs. 32% of the SC twins (24). The opposite-sex twin analyses, including only dizygotic twins, showed no difference in the risk of major malformations between ART and SC twins. Multiple pregnancies, which could be regarded as an adverse outcome of ART, have a higher risk of malformations than singleton pregnancies (25). We decided to exclude data on stillborn children due to different registration practices of stillbirths in the four countries during the study period and, with this, concerns about the data quality on malformations among stillborn. For the majority of children, we had a follow up beyond the neonatal period, which is essential for monitoring malformations (26).

Many factors potentially affect the development of the early embryo. Residual confounding by parental factors is possible, and the Nordic ART population has changed over time. Furthermore, the practice of registration of

Table 2. Major malformations in children born after assisted reproductive technology vs. spontaneous conception.

	Singletons						All (singletons + twins)					
	ART, *n* (%)	SC, *n* (%)	Crude OR[a]	95% CI	Adj.OR[b]	95% CI	ART, *n* (%)	SC, *n* (%)	Crude OR[a]	95% CI	Adj.OR[b]	95% CI
Nervous system	71 (0.12)	289 (0.08)	1.40	1.08–1.82	1.39	1.04–1.85	164 (0.18)	606 (0.13)	1.47	1.23–1.76	1.34	1.10–1.64
Eye	60 (0.10)	251 (0.07)	1.37	1.04–1.82	1.54	1.12–2.10	118 (0.13)	458 (0.09)	1.39	1.13–1.71	1.43	1.13–1.81
Ear, face, neck	169 (0.28)	819 (0.23)	1.20	1.02–1.41	1.22	1.02–1.47	277 (0.31)	1190 (0.25)	1.24	1.08–1.41	1.22	1.05–1.41
Heart	384 (0.63)	1742 (0.50)	1.25	1.11–1.39	1.18	1.05–1.33	732 (0.81)	3285 (0.68)	1.17	1.08–1.27	1.14	1.04–1.24
Respiratory	31 (0.05)	243 (0.07)	0.72	0.50–1.05	0.68	0.45–1.01	94 (0.10)	465 (0.10)	1.10	0.87–1.37	1.05	0.83–1.34
Oro-facial	81 (0.13)	419 (0.12)	1.10	0.86–1.39	1.03	0.79–1.34	122 (0.14)	656 (0.14)	0.99	0.81–1.21	0.94	0.76–1.16
Gastrointestinal	174 (0.28)	756 (0.22)	1.30	1.10–1.53	1.29	1.07–1.54	337 (0.37)	1445 (0.30)	1.22	1.08–1.38	1.17	1.03–1.34
Abdominal wall	7 (0.01)	92 (0.03)	0.43	0.20–0.94	0.63	0.28–1.41	12 (0.01)	154 (0.03)	0.41	0.23–0.75	0.48	0.26–0.90
Urinary	150 (0.24)	612 (0.17)	1.39	1.16–1.66	1.35	1.11–1.64	265 (0.29)	1116 (0.23)	1.31	1.14–1.50	1.20	1.04–1.39
Genital	176 (0.29)	847 (0.24)	1.16	0.98–1.36	1.09	0.91–1.30	307 (0.34)	1302 (0.27)	1.20	1.06–1.37	1.12	0.97–1.29
Musculo-skeletal	797 (1.30)	4153 (1.18)	1.14	1.06–1.22	1.11	1.03–1.20	1200 (1.33)	5361 (1.11)	1.15	1.08–1.22	1.06	1.00–1.13
Malformation	2100 (3.43)	10 223 (2.91)	1.16	1.11–1.22	1.14	1.08–1.20	3628 (4.02)	16 038 (3.33)	1.18	1.13–1.22	1.12	1.08–1.17
	Twins						Opposite-sex twins					
	ART, *n* (%)	SC, *n* (%)	Crude OR[a]	95% CI	Adj.OR[b]	95% CI	ART, *n* (%)	SC, *n* (%)	Crude OR[a]	95% CI	Adj.OR[b]	95% CI
Nervous system	93 (0.32)	317 (0.24)	1.23	0.94–1.60	1.13	0.86–1.48	47 (0.34)	91 (0.21)	1.47	0.98–2.21	1.30	0.86–1.97
Eye	58 (0.20)	207 (0.16)	1.18	0.85–1.64	1.13	0.80–1.60	25 (0.18)	69 (0.16)	1.01	0.60–1.73	0.97	0.56–1.68
Ear, face, neck	108 (0.37)	371 (0.28)	1.34	1.06–1.68	1.30	1.02–1.65	55 (0.40)	121 (0.28)	1.48	1.05–2.10	1.50	1.06–2.14
Heart	348 (1.20)	1545 (1.17)	0.84	0.74–0.96	0.83	0.73–0.95	174 (1.25)	430 (0.98)	1.09	0.89–1.33	1.07	0.87–1.31
Respiratory	63 (0.22)	222 (0.17)	1.20	0.89–1.61	1.19	0.87–1.62	26 (0.19)	72 (0.16)	0.96	0.59–1.57	0.95	0.57–1.56
Oro-facial	41 (0.14)	238 (0.18)	0.75	0.53–1.07	0.72	0.51–1.03	19 (0.14)	85 (0.19)	0.71	0.42–1.21	0.71	0.41–1.22
Gastrointestinal	163 (0.56)	691 (0.52)	0.88	0.72–1.06	0.87	0.72–1.06	81 (0.58)	198 (0.45)	1.03	0.77–1.38	1.07	0.80–1.44
Abdominal wall	5 (0.02)	62 (0.05)	0.35	0.13–0.94	0.34	0.13–0.95	2 (0.01)	13 (0.03)	0.64	0.11–3.82	0.52	0.09–3.06
Urinary	115 (0.40)	504 (0.38)	0.97	0.78–1.22	0.92	0.73–1.16	56 (0.40)	161 (0.37)	0.99	0.71–1.38	0.96	0.68–1.36
Genital	131 (0.45)	456 (0.35)	1.07	0.86–1.33	1.03	0.82–1.28	61 (0.44)	117 (0.27)	1.37	0.98–1.92	1.31	0.92–1.87
Musculo-skeletal	403 (1.39)	1209 (0.92)	1.05	0.94–1.17	0.91	0.81–1.02	182 (1.31)	522 (1.19)	0.94	0.80–1.11	0.86	0.72–1.01
Any malformation	1528 (5.28)	5822 (4.42)	1.01	0.94–1.08	0.95	0.88–1.01	728 (5.23)	1879 (4.30)	1.04	0.94–1.15	1.00	0.90–1.11

aOR, adjusted odds ratio; ART, assisted reproductive technology; CI, confidence interval; SC, spontaneous conception.

[a]Adjusted for parity (0 vs. ≥1) and year of birth.

[b]Adjusted for parity (0 vs. ≥1), year of birth, maternal age, child's sex and country.

Table 3. Risk of any major malformation in different time periods according to mode of conception and plurality.

	Any major congenital malformation							
	1988–1992				1993–1997			
	ART, *n* (%)	SC, *n* (%)	aOR[a]	95% CI	ART, *n* (%)	SC, *n* (%)	aOR[a]	95% CI
Singletons	49 (2.22)	272 (1.69)	1.36	0.96–1.91	234 (2.22)	1340 (1.97)	1.04	0.89–1.22
Twins	32 (2.28)	406 (1.85)	1.19	0.80–1.78	236 (3.58)	1144 (3.67)	0.87	0.74–1.02
All	81 (2.25)	678 (1.79)	1.16	0.90–1.50	470 (2.75)	2484 (2.50)	1.02	0.91–1.14
	1998–2002				2003–2007			
	ART, *n* (%)	SC, *n* (%)	aOR[a]	95% CI	ART, *n* (%)	SC, *n* (%)	aOR[a]	95% CI
Singletons	697 (3.57)	3734 (3.15)	1.13	1.03–1.23	1119 (3.87)	4858 (3.29)	1.16	1.08–1.24
Twins	634 (5.59)	1634 (4.95)	1.02	0.91–1.14	625 (6.53)	2288 (6.29)	0.91	0.82–1.01
All	1331 (4.31)	5368 (3.54)	1.17	1.10–1.26	1744 (4.53)	7146 (3.89)	1.12	1.05–1.18

aOR, adjusted odds ratio; ART, assisted reproductive technology; CI, confidence interval; SC, spontaneous conception.
[a]Adjusted for parity (0 vs. ≥1), year of birth, maternal age, child's sex and country.

congenital malformations has been gradually improved in some of the Nordic countries, which has led to an increase in the overall number of malformations registered per year. An increased risk of malformations in children conceived after ART is biologically plausible but the major challenge when assessing the association between ART and malformations is a sufficient sample size, as malformations are rare events. The complexity of both the exposure and the outcome, combined with the difficulties of grouping embryological heterogeneous malformations, challenge both the study design and the sample size (14,16,27). An ideal control group might consist of women referred for ART but who become pregnant spontaneously while waiting for treatment. However, such a control group of sufficient sample size is difficult to establish. Otherwise a sibling design where one sibling is conceived after ART and the other sibling after SC could be valuable. This design would enable the maternal contribution, and thus the effect of subfertility, to be held steady, while the effect of the in vitro procedures could be more clearly investigated. Nonetheless, with the existing evidence, there is no doubt that the characteristics of the subfertile couples matters, as several studies have shown that couples who conceive spontaneously, but with a time to pregnancy of more than one year, have an increased risk of malformations (28).

To explore the underlying mechanisms or associations between ART and specific malformations, new classification systems based on pathology or etiology rather than organ system have been suggested (7). Blastogenesis is the developmental stage of the embryogenesis with fertilization, cleavage and germ layer formation. By grouping malformations originating from these first four weeks of embryo development, it is hypothesized that such malformations are more likely to be a result of the ART procedures compared with malformations originating later in pregnancy. However, all four Nordic countries have used the ICD system during the study period, and because we decided to include only major malformations and furthermore restrict our analyses to live-births, our data were unfortunately unsuitable for analyzing the risk of blastogenesis malformations.

Data on important treatment characteristics such as embryo culture media, day of embryo transfer and medication used for hormonal stimulation were not available in the Nordic ART registries during the study period. Since our data included only pregnancies resulting in a registered live-birth, we do not have data on stillbirth on elective terminations of pregnancies after prenatal diagnosis of a malformation. The rate of elective terminations due to malformations may differ between ART and SC children, and potentially bias the study findings in either direction (29). A Finnish study found the frequency of elective terminations due to malformations among women pregnant after ART to be equal to that of the general population (22). This was supported by a recent French study on congenital heart malformation after ART. They found that malformation data on live-born children are most likely adequate when assessing the risk of malformations, as they did not find a difference in the rate of pregnancy terminations between ART and SC after identification of severe congenital heart malformations (30). A potential reporting bias for ART children seems unlikely, since only major malformations were included in this study and would therefore be expected to be detected regardless of mode of conception.

In conclusion, the relative risk of major congenital malformations between ART and SC children remained unchanged throughout the study period. The absolute risk increased, however, after both types of conception, which is in contrast to the declining rates of other adverse neonatal outcomes among ART children. Where the increasingly younger and less reproductive population of couples undergoing ART has resulted in an overall better perinatal outcome, this does not seem to have influenced the risk of major malformations in ART children in the same way. This indicates that the etiology behind congenital malformations is different and remains unclear. Although an absolute increase in malformations was found for both ART and SC children, we believe that this is most likely attributable to changes in data quality, registration and ascertainment of malformations that have occurred over the last two decades. Couples seeking fertility treatment should be informed about the slightly increased risk of malformations in children conceived after ART but should not be discouraged from attempting to have their own children, as the overall risk of having a child with a major malformation is low.

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Supporting information

Additional Supporting Information may be found in the online version of this article:

Table S1. Data flowchart. National cohorts and malformation registries.